Efficacy of SBP-101 Against Human Pancreatic Ductal Adenocarcinoma Following Orthotopic Implantation of L3.6pl Pancreatic Cancer Cells into Nude Mice

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ABSTRACT

Background:
SBP-101 is an analogue of the native polyamine (PA), spermine. Increases in polyamine biosynthesis in a number of neoplasms, including pancreatic ductal adenocarcinoma (PDA), suggest this to be a promising therapeutic target. These studies examined the anti-neoplastic effects of subcutaneous administration of SBP-101 following orthotopic implantation of human L3.6pl pancreatic cancer cells into the pancreas of nude mice.
Methods:
L3.6pl cells were injected into the pancreas of nude mice; treatment was initiated by group (n = 10/group planned) 7-10 days later following establishment of tumors:
Study 1: saline (control), SBP-101 (25 mg/kg), SBP-101 (50 mg/kg), and SBP-101 (100 mg/kg) daily (QD) for 4 to 6 weeks (wks).
Study 2: saline (control), SBP-101 (25 mg/kg QD), SBP-101 (25 mg/kg 3 x/wk), SBP-101 (15 mg/kg 3x/wk), and SBP-101 (5 mg/kg 3x/wk) for 4 to 6 wks.
Study 3: saline (control), gemcitabine (GEM) (100 mg/kg 2x/wk, intraperitoneally), SBP-101 (25 mg/kg 3x/wk), and SBP-101 + GEM for 4 to 6 wks.
Results:
In Study 1, the 25mg/kg QD dosing regimen resulted in an 82.9% reduction in pancreas weight in tumor bearing mice. Doses of 50 and 100 mg/kg resulted in earlier deaths and proved to be toxic. Histologic changes in the liver included hepatocyte reparative change and, in the exocrine pancreas, a mild decrease of cytoplasmic granules in the epithelium of the pancreatic acini. No histologic effects were seen in the endocrine pancreas.
In Study 2, the 25 mg/kg QD dosing regimen resulted in a 72.7% and 81.4% reduction in pancreas weight and tumor volume, respectively, while the 25 mg/kg 3x/wk dose group resulted in a 47.8% and 66.6% reduction. Dose-related decreases in pancreas weight and tumor volume (20.1% and 52.6%, respectively) were also observed at 15 mg/kg; no decreases were noted at 5 mg/kg. Median survival was 32 days with 25 mg/kg QD and 42 days with 25 mg/kg 3x/wk compared with 21 days in the control group.
In Study 3, treatment with GEM, SBP-101, and SBP-101 + GEM resulted in 18.7%, 35.6%, and 42.4% decreases in body weight, respectively. Compared with controls, treatment with GEM, SBP-101, and GEM + SBP-101 resulted in 24.7%, 58.8%, and 67.2% decreases in pancreas weight, and 37.8%, 58.4%, and 72.9% decreases in tumor volume, respectively, suggesting a synergistic or additive effect with combination treatment. The incidence of liver metastasis was also decreased in all three treatment groups.
Conclusions:
SBP-101 25 mg/kg administered QD or 3x/wk inhibited the growth of human pancreatic ductal adenocarcinoma and prolonged survival in mice. Co-administration of SBP-101 with gemcitabine appeared to have an additive or synergistic effect on reduction in the pancreatic tumor. These results support the clinical development of SBP-101 for pancreatic cancer.

INTRODUCTION

- SBP-101 is an analogue of the naturally occurring polyamine (PA), spermine.
- The polyamine transport uptake mechanism appears to be up-regulated in various tumor types, including pancreatic ductal adenocarcinoma (PDA).
- Inducing polyamine depletion via the cellular uptake of synthetic polyamine analogues has been proposed as an antitumor strategy, making SBP-101 a promising therapeutic target.[1-4]

OBJECTIVES

- The anti-neoplastic effects of SBP-101 after subcutaneous (SC) administration were evaluated using human pancreatic cancer cells (L3.6pl) grown orthotopically in the pancreas of nude mice.[5-9] The objectives of the three studies were as follows:
- **Study 1**: to determine the efficacy and tolerability of daily (QD) doses of SBP-101 (25, 50, and 100 mg/kg) for 4 to 6 weeks in tumor-bearing and non-tumor-bearing nude mice.
- **Study 2**: to determine the efficacy and tolerability of 3x/weekly dosing of SBP-101 (5, 10, and 25 mg/kg) for 4 to 6 weeks in tumor-bearing and non-tumor-bearing nude mice.
- **Study 3**: to determine the efficacy and tolerability of SBP-101 (25 mg/kg 3x/week) in combination with gemcitabine (Gemzar; 100 mg/kg intraperitoneally 2x/week) for 4 to 6 weeks in tumor-bearing mice

METHODS

- One million L3.6pl pancreatic cancer cells were injected into the pancreas of mice and tumors were allowed to develop over 7-10 days.
- Non-tumor-bearing (NTB) nude mice served as controls in Studies 1 and 2 and were not injected with L3.6pl cells. The control mice were treated in the same way as the tumor-bearing mice (TB).
- In Study 3 all mice were TB; saline-treated TB mice served as controls.
- In all studies 10 mice per treatment group were planned.

Dose Groups

Group	Dose
Study 1	
Control	Saline
SBP-101	25 mg/kg QD
SBP-101	50 mg/kg QD
SBP-101	100 mg/kg QD
Study 2	
Control	Saline
SBP-101	5 mg/kg 3x/wk
SBP-101	15 mg/kg 3x/wk
SBP-101	25 mg/kg 3x/wk
SBP-101	25 mg/kg QD
Study 3	
Control	Saline
SBP-101	25 mg/kg 3x/wk
Gemcitabine	100 mg/kg 2x/wk
SBP-101 + Gemcitabine	25 mg/kg 3x/wk 100 mg/kg 2x/wk

RESULTS

Percent (%) Decrease in Pancreatic Weight

	Study 1			Study 2				Study 3		
	SBP-101 25 mg/kg QD	SBP-101 50 mg/kg QD	SBP-101 100 mg/kg QD	SBP-101 5 mg/kg 3x/wk	SBP-101 15 mg/kg 3x/wk	SBP-101 25 mg/kg 3x/wk	SBP-101 25 mg/kg QD	SBP-101 25 mg/kg 3x/wk	Gemcitabine 100 mg/kg 2 x/wk	SBP-101 25 mg/kg 3x/wk + Gemzar 2 x/wk
Non Tumor-bearing	44.3	48.4	47.3	-4.4	14.4	20.6	40.6	NA	NA	NA
Tumor-bearing	**82.9**	**91.0**	**87.8**	**-8.9**	**20.1**	**47.8**	**72.7**	**58.8**	**24.7**	**67.2**

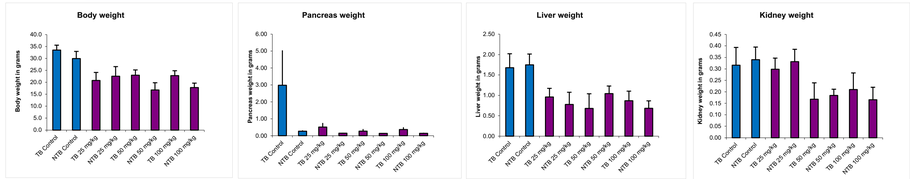
Study 1: Histologic Results in Tumor-bearing Mice

Dose Group (Representative TB Mouse)	Incidence of Liver Metastases†	Reparative Change in Liver (No. of observations†)	Decrease of Exocrine Pancreatic Granules (No. of observations†)
No drug (Mouse no. 7)	4 out of 7	----	----
25 mg/kg QD (Mouse no. 4)	2 out of 4	none	3 out of 4
50 mg/kg QD (Mouse no. 7)	1 out of 7	4 out of 7	2 out of 7
100 mg/kg QD (Mouse no. 7)	1 out of 7	7 out of 7	2 out of 7

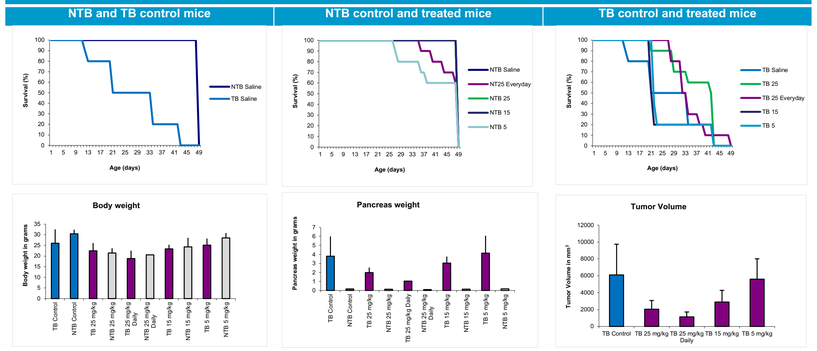
† Reflects the number of cross sections of a given tissue sample where metastases or change was noted out of total number of sections evaluated

RESULTS

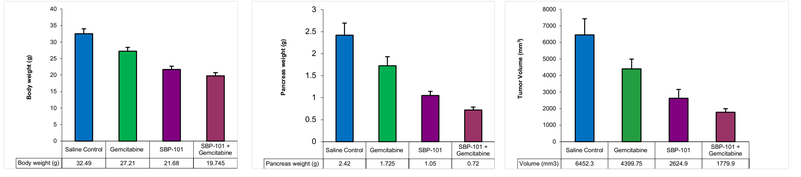
Study 1: Body Weight, Pancreas Weight, Liver Weight, Kidney Weight



Study 2: Survival, Body Weight, Pancreas Weight, Tumor Volume



Study 3: Body Weight, Pancreas Weight, Tumor Volume



CONCLUSIONS

- Administration of graduated doses of SBP-101 resulted in inhibition of pancreatic tumor growth and decreased metastasis to other organs; the 5 mg/kg dose was found to be ineffective.
- All tumor-bearing mice that received SBP-101 at 15, 25, 50 and 100 mg/kg doses (Studies 1 and/or 2) demonstrated decreases in pancreas weights and volume of tumors (Study 2) compared with the matching controls without SBP-101.
- The optimal biological dose of SBP-101 was determined to be 25 mg/kg daily or 3x/week based on inhibition of tumor growth, drug tolerance, survival, and histologic effects.
- Co-administration of SBP-101 25 mg/kg 3x/week with gemcitabine 100 mg/kg dose 2x/week appeared to have an additive or synergistic effect on the reduction in pancreatic tumor.
- These results support the clinical development of SBP-101 for pancreatic cancer.

REFERENCES
1. Hector S, et al. Cancer Chemother Pharmacol 2008;62:517–527. 2. Jänne J, et al. Biochim Biophys Acta 1978;473:241–293. 3.Porter CW, et al. Adv Enz Reg 1988;27:57–79. 4.Casero RA Jr, et al. Biochem Soc Trans 2003;31:361–365. 5. Bruns CJ, et al. Neoplasia, 1999, 1:50-62. 6. Baker CH, et al. Int J Clin Oncol. 2001;6:59-65. 7.Baker CH, et al. Cancer Res. 2002;62:1996-2003. 8.Baker CH, et al. Int J Clin Oncology. 2006;29:125-38. 9. Konduri SD, et al. Clin. Cancer Res 2009:15:6087-6095.

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